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Potential role of ultrafine particles in associations between airborne particle mass and cardiovascular health

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Abbreviations:

BP : blood pressure

CAP: concentrated ambient particles

CIMT: carotid intima-media thickness

CI: confidence interval

CHD: coronary heart disease

CHF: congestive heart failure

COPD: chronic obstructive pulmonary disease

DEP: Diesel exhaust particles

EC: elemental carbon

ETS: environmental tobacco smoke

HR: heart rate

HRV: heart rate variability

IL-1β: interleukin 1beta

IL-6: interleukin 6

$NC_{0.01\text{-}0.1}$: number concentrations of ultrafine mode particles 0.01 to 0.1 μm in diameter

$NC_{0.1\text{-}1}$: number concentrations of accumulation mode particles 0.1 to 1.0 μm in diameter

NFκB: nuclear transcription factor-κB

NMMAPS: National Morbidity, Mortality and Air Pollution study

Odds ratio: OR

PAH: polycyclic aromatic hydrocarbon

PM: particulate matter

$PM_{2.5}$: particulate matter < 2.5 μm in aerodynamic diameter

PM_{10}: particulate matter < 10 μm in aerodynamic diameter

PN: particle number

ROS: reactive oxygen species

RR: relative risk

TNF-α: tumor necrosis factor-α

TSP: total suspended particulates (PM approximately < 50 μm in diameter)

UFP: ultrafine particulate matter, < 0.1 μm in aerodynamic diameter

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OUTLINE OF MANUSCRIPT SECTION HEADERS:

ABSTRACT

Numerous epidemiologic time series studies have shown generally consistent associations of cardiovascular hospital admissions and mortality with outdoor air pollution, particularly mass concentrations of particulate matter (PM) < 2.5 or < 10 μm in diameter ($PM_{2.5}$, PM_{10}). Panel studies with repeated measures have supported the time series results showing associations between PM and risk of cardiac ischemia and arrhythmias, increased blood pressure, decreased heart rate variability, and increased circulating markers of inflammation and thrombosis. The causal components driving the PM associations remain to be identified. Epidemiologic data using pollutant gases and particle characteristics such as particle number concentration and elemental carbon has provided indirect evidence that products of fossil fuel combustion are important. Ultrafine particles < 0.1 μm (UFP) dominate particle number concentrations and surface area, and are therefore capable of carrying large concentrations of adsorbed or condensed toxic air pollutants. It is likely that redox active components in UFP from fossil fuel combustion reach cardiovascular target sites. High UFP exposures may lead to systemic inflammation through oxidative stress responses to reactive oxygen species, and thereby promote the progression of atherosclerosis and precipitate acute cardiovascular responses ranging from increased blood pressure to myocardial infarction. The next steps in epidemiologic research are to identify more clearly the putative PM casual components and size fractions linked to their sources. To advance this, we discuss in a companion paper (Sioutas et al. in press) the need for and methods of UFP exposure assessment.

Importance

Coronary heart disease (CHD) is the leading cause of death and hospitalization among adults 65 years of age or older (Desai et al. 1999), which makes the identification of preventable causes for heart disease morbidity and mortality an important research goal. Numerous epidemiologic time series studies have shown generally consistent associations of outdoor (ambient) air pollution with cardiovascular hospital admissions (Burnett et al. 1995; 1997a; 1997b; 1999; D'Ippoliti et al. 2003; Le Tertre et al. 2002; Linn et al. 2000; Mann et al. 2002; Morris et al. 1995; Peters et al. 2001a; Poloniecki et al. 1997; Samet et al. 2000a; Schwartz and Morris 1995; Schwartz 1999; Zanobetti et al. 2000a; 2000b; 2001). Consistent associations of ambient air pollution have also been found with cardiovascular mortality (Clancy et al. 2002; Dockery et al. 1993; Goldberg et al. 2001a, 2001b; Hoek et al. 2001; Kwon et al. 2001; Laden et al. 2000; Pope et al. 2004a; Rossi et al. 1999; Samet et al. 2000b; Schwartz et al. 1996; Wichmann et al, 2000; Zanobetti et al. 2003). The National Research Council's (NRC) Committee on Research Priorities for Airborne Particulate Matter (PM) has identified research priorities to explain the morbidity and mortality associations in the time series studies (NRC, 1998; 1999; 2001; 2004). One priority is to identify the pathophysiological mechanisms and causal pollutant components driving these associations (Seaton et al. 1995).

The causal components driving the PM relationship to cardiovascular morbidity and mortality remain to be identified. Historically, the difficulty in accomplishing this in epidemiologic studies is related to the common use of ambient air pollution data from monitoring stations located at central regional sites. This has led to both exposure misclassification and high correlations between different pollutants. Both of these problems can be addressed with measurements of personal and/or microenvironmental exposures (Sarnat et al. 2000; 2001). Another problem is that the importance of particle size and chemistry has been limited by reliance on the same government

monitoring data. In the U.S., this data generally only includes particle mass concentrations in air at two particle size cuts, PM_{10} (PM < 10 μm in aerodynamic diameter) and more recently $PM_{2.5}$ (PM < 2.5 μm). However, there is sufficient reason to believe that ultrafine particles (PM < 0.1 μm) are important in morbidity and mortality associations otherwise attributed to larger size fractions.

Major characteristics of ultrafine particles (UFP) that support their potential importance include a high pulmonary deposition efficiency, magnitudes higher particle number concentration than larger particles and thus a much higher surface area. The ultrafine particle's surface can carry large amounts of adsorbed or condensed toxic air pollutants (oxidant gases, organic compounds and transition metals) (Oberdörster 2001). Many of these toxic air pollutants have been identified as having pro-inflammatory effects in part through the action of reactive oxygen species (ROS), but relevant exposure data is rarely available to epidemiologists. Available surrogate measures of fossil fuel combustion such as elemental carbon (EC) or black smoke are of some use in this regard. Results from a study in southern California showed a large proportion of urban UFP is made up of primary combustion products from mobile source emissions (particularly diesel and automobile exhaust), and includes organic compounds, EC and metals (Kim et al. 2002). Because exposure to mobile emissions can be variable across short distances and depends on personal activity patterns, assessing such exposures requires methods that go beyond the use of government monitoring data alone. These issues regarding the characteristics of UFP are more thoroughly discussed in a companion paper (Sioutas et al. in press)

In the present review, we discuss evidence for adverse effects of air pollution on cardiovascular health with an emphasis on findings that suggest a role for UFP and related toxic air pollutant components. To date, there is little direct epidemiologic data on UFP. Studies using other particle size fractions, other particle measurements such as black smoke, and gas-phase pollutants

are used to provide a rationale for investigations of UFP. The focus of this paper is on epidemiologic studies following individual subjects over time. Several excellent reviews of experimental data and methods can be found elsewhere (Donaldson et al. 2001; Utell et al. 2002).

Evidence of Causal Pollutant Components in Epidemiologic Time Series, Cohort and Cross-sectional Studies

The National Morbidity, Mortality and Air Pollution study (NMMAPS) is the largest of the air pollution time series studies to date (Samet et al. 2000a; 2000b). Results show positive associations of PM_{10} with cardiopulmonary mortality and with hospital admissions for cardiovascular disease, chronic obstructive pulmonary disease (COPD) and pneumonia in patients 65 years of age and older living in varied environments across up 90 cities in the U.S. A subsequent analysis to correct for statistical errors showed an increase of 0.34% (95% CI: 0.1, 0.57) in combined cardiorespiratory mortality for each 10 $\mu g/m^3$ of air increase in PM_{10} (Dominici et al. 2003). Another reanalysis of hospitalizations in 14 U.S. cities by Janssen et al. (Janssen et al. 2002) broke down the PM_{10} concentrations using information on source categories. They found that for cardiovascular admissions, and to a lesser extent COPD admissions, PM_{10} from highway vehicle and diesel emissions and from oil combustion showed the strongest associations with the most stable regression coefficients in co-regressions with other source categories. These findings are supported by an analysis of PM data collected for the Harvard Six Cities Study (Dockery et al. 1993) by Laden et al. (2000) using elemental profiles of $PM_{2.5}$ samples. They showed that associations between mobile source (largely traffic-related) particles and daily total mortality for the six metropolitan areas were twice that for sulfate-rich coal combustion particles. This difference was most clearly demonstrated for deaths from CHD.

Additional information regarding causal pollutant components has come from analyses of ambient gaseous air pollutants under U.S. federal regulation (CO, NO_2, SO_2 and O_3). They can be strongly correlated with PM in ambient air. A European study by Katsouyanni et al. (2001) of 29 cities showed a positive association between total mortality and PM_{10}, and this association was not confounded by SO_2 or O_3. However, they did find that in cities with higher versus lower average NO_2, the association with PM_{10} was significantly greater (0.80 vs. 0.19% increase in mortality per 10 $\mu g/m^3$ PM_{10}, respectively). The NMMAPS study found PM_{10} associations with mortality were largely independent of NO_2, SO_2 and O_3 (Samet et al. 2000a). Goldberg et al. (2001a, 2001b), Moolgavkar et al. (2000), and Venners et al. (2003) have also found robust associations between cardiovascular mortality and pollutant gases that were often are stronger than particle associations. In a time series study of the Los Angeles air basin, Linn et al. (2000) found significant associations of daily cardiovascular hospital admissions were strongest for CO, followed by NO_2 then much weaker associations for PM_{10}, but daily PM data were limited by fewer stations. Morris et al. (1995) and Morris and Naumova (1998) found hospital admissions for congestive heart failure (CHF) were associated with CO independent of other gaseous pollutants in several large U.S. cities. Mann et al. (2002) also found significant associations of daily CHD hospital admissions with NO_2 and CO in Los Angeles, particularly among cases with a secondary diagnosis of CHF or arrhythmia. Lin et al. (2003) found that an interquartile range increase in CO was associated with an increase of 6.4% in daily angina and acute MI emergency room visits in Sao Paulo, Brazil. A time series study of seven European areas found cardiovascular hospital admissions, especially CHD, were associated with SO_2 (Sunyer et al. 2003). Associations between gases and hospital admissions for CHD and CHF have been found in several other studies (e.g., Burnett 1997b; 1999; Koken et al. 2003; Morris et al. 1995; 1998).

Some of the time series investigators have hypothesized that pollutant gases could be acting as indicators for a causal mixture of pollutants including PM-related components. Ambient CO is highly correlated with UFP near combustion sources such as freeways (discussed more fully below). Although it is possible that some of the effects detected with CO are due to the formation of carboxyhemoglobin in the blood and carboxymyoglobin in muscle, reported ambient concentrations are low (< 6 ppm). A postulated mechanism for increased susceptibility to low CO doses is the attainment of a nominal threshold of reduced O_2 transport to the heart and further compromised cardiac myoglobin, particularly in CHF patients (McGrath, 2000).

Additional evidence of causal components linked to UFP come from European studies that have used a non-gravimetric PM measure called black smoke, which is roughly representative of EC. Le Tertre et al. (2002) conducted a time series analysis of cardiovascular hospital admissions in eight European cities and found that CHD admissions were associated with PM_{10} and black smoke. The association with PM_{10}, but not with black smoke, was reduced by adding CO to the model and eliminated by adding NO_2. Both Le Tertre et al. (2002) and the European study by Katsouyanni et al. (2001) reported above, hypothesized that their results were attributable to traffic exhaust and its consequent high emissions of CO, NO_2, black smoke, and air toxics. It is relevant to point out that traffic exhaust, particularly from diesel engines, is a major contributor to ultrafine particle mass in urban areas (Kittelson, 1998; Tobias et al. 2001) and in general, UFP are both strongly linked to mobile source emissions and laden with toxic constituents (Shi et al. 2001; Kim et al. 2002).

While time series investigations have provided important information regarding the overall public health impact of ambient air pollutants on severe outcomes such as mortality, studies of individual subjects have provided insights into the underlying acute or chronic exposure-response

relationships. Below we review studies of individuals using various epidemiologic designs, including cohort and panel studies, focusing only on findings for cardiovascular outcomes. Details for selected studies are presented in Table 1 and follow the discussion in the text.

Time series studies have provided evidence for acute effects of air pollutants on cardiovascular morbidity and mortality. However, there are still gaps in the literature regarding chronic health impacts from long-term pollutant exposures. Cohort studies are best suited to address this gap. Dockery et al. (1993) reported evidence from the Harvard Six Cities study that ambient $PM_{2.5}$ was associated with risk of cardiopulmonary mortality in a cohort of 8,111 adults (Table 1). Pope et al (2004a) used 16 years of data from over 500,000 adults in 151 U.S. cities who participated in the American Cancer Society II cohort. The authors found that a 10 $\mu g/m^3$ elevation in $PM_{2.5}$ was associated with 8-18% increases in mortality due to ischemic heart disease, dysrhythmias, heart failure, and cardiac arrest. Mortality from various respiratory causes was not associated with $PM_{2.5}$ (Table 1). In contrast, in a cohort study of 6,338 Seventh Day Adventists living in California, found associations of long-term exposure to PM and O_3 with respiratory mortality, but not with cardiovascular mortality (Abbey et al. 1999) (Table 1). Differences in findings might be due to exposure misclassification from the use of central regional air pollutant data. Hoek et al. (2002) tried to address this issue by evaluating effects of traffic exposures near the home in a cohort study of 5,000 adults followed 8 years in the Netherlands (Table 1). They showed that living near a major road was more strongly associated with cardiopulmonary mortality than ambient background air pollutant levels. This finding suggests that pollutants more closely associated with traffic, which include UFP and associated toxic air pollutants, could be causal components in the mortality associations.

Kunzli et al (2004) conducted a cross-sectional study of 798 healthy adults with elevated LDL-cholesterol or homocysteine living on Los Angeles (Table 1). Subjects were in a dietary supplement clinical trial with ultrasound data on carotid intima-media thickness (CIMT) as an estimate of atherosclerosis. Exposure included an estimate of using a geostatistical models to link subject address to annual mean $PM_{2.5}$ from 23 local air monitoring stations. They found positive associations between CIMT and $PM_{2.5}$, adjusting for host risk factors. Associations were larger for women, older subjects (≥ 60), subjects on lipid lowering medications, and never smokers.

Evidence for Pathophysiological Mechanisms and Causal Components in PM-related Cardiovascular Effects

The following section looks at epidemiologic studies called panel studies, which are designed to evaluate the relationship between repeated air pollutant exposures and cardiovascular outcomes in individual subjects. We augment this discussion with a few selected human clinical studies that extend the panel studies findings using controlled exposures, particularly those that aim to replicate ambient air mixtures. The discussion is divided by related groups of cardiovascular outcomes.

Cardiac Ischemia and Related Outcomes

Only one published study to our knowledge has examined evidence for the relationship of particulate air pollutant exposure to cardiac ischemia in humans. An epidemiologic study of 45 adults with stable CHD conducted by Pekkanen et al. (2002) analyzed data from repeated biweekly in-clinic ECG measurements during submaximal exercise testing and outdoor ultrafine and fine particles measured at a central regional site of Helsinki, Finland (Table 1). They found significant associations between risk of ST segment depression and ambient $PM_{2.5}$ mass, number

concentrations of ultrafine mode particles 0.01 to 0.1 μm in diameter ($NC_{0.01-0.1}$) and number concentrations of accumulation mode particles 0.1 to 1.0 μm in diameter ($NC_{0.1-1}$) (Table 1). Odds ratios were around 3.0 for all particle metrics for an increase around their interquartile distribution. Smaller but significant associations were also found for the gases NO_2 and CO, which were moderately correlated with the co-located particle measurements. The association with ultrafine particle number concentration was independent of $PM_{2.5}$ mass concentration. It is surprising that associations for outdoor ambient $NC_{0.01-0.1}$ were as strong as $PM_{2.5}$ given the expectation that human exposure to UFP is less consistently represented by central site PM monitoring than $PM_{2.5}$, which shows much lower spatial variability than UFP (reviewed by Pekkanen and Kulmala 2004; and Sioutas et al. in press).

Cardiorespiratory symptoms potentially related to cardiac ischemia were assessed by de Hartog et al (2003) in elderly patients with CHD. The authors found that although chest pain was not associated with PM exposure, a 10 $\mu g/m^3$ increase in ambient $PM_{2.5}$ was associated with shortness of breath and avoidance of activities (Table 1).

A case-crossover study of 691 subjects from the Augsburg Myocardial Infarction Registry found a two to three times increased risk of myocardial infarction (MI) for time-activity diary reports of hours exposed to traffic, particularly for times spent in cars and public transportation in the hours leading up to cardiac symptom onset (Peters et al. 2004) (Table 1). No direct air pollutant measurements were available. However, as discussed in our companion paper, exposures to UFP can be magnitudes higher than background levels within vehicles and near busy highways, and to a much greater degree than larger particles (Sioutas et al. in press). Accumulation mode PM, volatile organic compounds and gases such as CO could have also played a role in the findings of Peters et al. (2004).

Blood Pressure (BP)

Two studies showing associations between air pollution and BP followed subjects with COPD (Linn et al. 1999; Brauer et al. 2001, Table 1). Linn et al. (1999) found that for only 120 total person-observation times in 30 subjects, an increase of 33 $\mu g/m^3$ ambient PM_{10} (study mean) was associated with a 5.7 mm Hg increase in systolic BP. In contrast, Brauer et al. (2001) found systolic BP was inversely, but weakly associated with personal $PM_{2.5}$ in a pooled regression analysis of 16 subjects with COPD monitored on seven separate days. This association was not confounded by inverse associations with ambient CO. Inverse associations with ambient PM_{10} were larger, but confounded by CO. Another study examined 2,607 German adults less than 65 years of age evaluated on two occasions three years apart and found a positive association of systolic BP with ambient concentrations of both total suspended particulates (TSP) and SO_2 (Ibald-Mulli et al, 2001) (Table 1).

Ibald-Mulli et al. (2004) conducted one of the few panel studies to focus on the relationship between UFP and BP (Table 1). They followed 131 adults with CHD in three European centers every two weeks for around 11 clinic visits. An increase of a 5-d average of 10,000/cm^3 ultrafine particles ($PM_{0.01-0.1}$) was associated with small decrease in systolic BP (–0.72 mm Hg, $p < 0.01$) and diastolic BP (–0.70 mm Hg, $p < 0.01$). Comparably small associations were also found for CO, 1,000/cm^3 of accumulation mode particles and 10 $\mu g/m^3$ $PM_{2.5}$. Authors hypothesized that BP medications in these CHD patients might have blunted or modified the response to air pollution exposure. However, these results contrast those of a panel study by Zanobetti et al. (2004), who found ambient 5-d average $PM_{2.5}$ was positively associated with blood pressure among 62 patients with pre-existing heart disease, using data from 631 repeated visits for cardiac rehabilitation in Boston (Table 1).

Panel study results for $PM_{2.5}$ can be compared to two experimental human studies (Brook et al., 2002; Gong et al. 2003; not shown in Table 1). Gong et al. (2003) studied the effects of $PM_{2.5}$ concentrated ambient particles (CAP) from Los Angeles air versus clean air on systolic BP in 12 healthy versus 12 asthmatic adults using a 2-hr rest-exercise exposure period in a chamber. CAPs are used to approximate the effects of "real world" particles. They found inverse associations of $PM_{2.5}$ CAP with systolic BP in asthmatics, but positive associations in healthy subjects. Results from two small studies by Brauer et al. (2001) and Gong et al. (2003) with relatively good exposure data show that $PM_{2.5}$ mass is inversely associated with BP in subjects with obstructive lung diseases. Brook et al., (2002) also studied the vascular effects of 150 $\mu g/m^3$ $PM_{2.5}$ CAP from Toronto air, adding 120 ppb O_3, in 25 healthy adults using a 2-hr exposure period in a chamber. They found a significant but small 0.1 mm decrease in brachial artery diameter by ultrasonography for the joint exposures versus filtered air, but no change in BP, flow-mediated diameter (endothelium dependent) or nitroglycerin-mediated dilatation (endothelium independent). A follow-up analysis showed that the organic and elemental carbon fraction of $PM_{2.5}$ CAP were significant determinants of the effects on brachial artery diameter, which is a more sensitive biomarker of effect than BP (Urch et al. 2004).

Potential mechanisms for the observed PM-associated increases in BP have been suggested to include an increase in sympathetic tone and/or the modulation of basal systemic vascular tone due to increased concentrations of a plasma peptide known as endothelin-1 (Ibald-Mulli et al, 2001). Endothelin-1 has multiple cardiovascular actions, including vasoconstriction, leading to maintenance of basal vascular tone and BP (Haynes and Webb, 1998) and accentuating BP elevation in more severe, sodium-sensitive hypertension (Schiffrin, 2001). It is directly associated with the severity of CHF and risk of subsequent cardiac death in CHF patients (Tsutamoto et al.

1995; Galatius-Jensen et al. 1996). Endothelin-1 is produced and cleared in the lung and is generated in response to the presence of ROS (free radicals) and their metabolites (Haynes and Webb, 1998). This leaves open the possibility that pollutants could induce an excess production of endothelin-1. Supporting evidence is that urban particles have been shown to increase endothelin-1 in rats (Bouthillier et al. 1998). Effects of endothelin-1 are partly counterbalanced by vasodilatory influences of endothelial NO (Vanhoutte, 2000). Endothelial NO synthase produces NO, which traverses the extracellular space to induce smooth muscle relaxation in the vessel wall. One ROS that can be produced in the presence certain pollutant components is superoxide, which can react with NO to form the potent oxidant, peroxynitrite. Peroxynitrite is likely involved in lipid peroxidation (O'Donnell & Freeman, 2001). Therefore, an additional potential mechanism whereby pollutant components can increase BP includes superoxide-mediated inhibition of the actions of NO in inducing vasodilatation.

Despite the above data on potential biological mechanisms, epidemiologic studies reviewed have found both a decrease and increase in BP in relation to air pollutant exposures. This may be because of differences between subject populations, differences in the types of regional air pollutants, or possibly due to medications used or underlying pathology (healthy, COPD, asthma, CHD, etc). There is also a lack of data in most studies on other influences on blood pressure, namely emotional states and physical activity, which could have sustained influence on non-ambulatory BP measurements. The above factors could result in contrasting shifts in sympathetic and vagal tone in response to inhaled air pollutants, or contrasting shifts in the balance between mediators such as endothelin-1 and endothelial NO. The time course of exposure-response relationships is also ill defined, particularly periods of exposure averaging times range from minutes to days. None of the epidemiologic studies used ambulatory BP monitoring to assess acute effects

of real time changes in exposure. Ambulatory BP monitoring is more closely associated with end organ damage (heart, kidney, brain) than isolated SBP or DBP readings taken in clinic offices (Mancia and Parati 2000).

Autonomic Control of Cardiac Rhythm

Heart rate variability (HRV) is a widely used non-invasive method to investigate cardiovascular autonomic control. Reduced HRV has been shown to be a predictor of increased mortality after a myocardial infarction (Kleiger et al. 1987; La Rovere et al. 1998) and has been related especially to sudden arrhythmic death (Odemuyiwa et al. 1991, Hartikainen et al. 1996). Fourier analysis of HRV can show the magnitude of variance in the heart's rhythm across different frequency bands. Different autonomic influences on cardiovascular function (heart rate and BP) are reflected by different frequency bands. The high frequency band (0.15-0.40 Hz) has been used to estimate cardiac vagal control and is linked to respiratory influences (Task Force, 1996). Lower frequencies (0.04-0.15 Hz) are believed to represent mixed sympathetic and parasympathetic influences (Task Force, 1996). Time domain measurements are also employed (described below).

One controlled exposure study showed significant decreases in HRV in 10 healthy elderly adults for 2 h exposures to CAPS from Chapel Hill, NC (mostly mobile source), as compared with clean air, and the decrease persisted 24h later (Devlin et al. 2003). In epidemiologic studies discussed below, ambient PM has been associated with decreased heart rate variability (HRV) (Peters et al. 1999; Pope et al. 1999; Liao et al. 1999; Gold et al, 2000; Creason et al. 2001; Magari et al. 2001; 2002a, 2002b; Chan et al, 2004; Holguin et al, 2003, Pope et al, 2004b), and cardiac arrhythmia (Peters et al. 2000). Only two studies to our knowledge have investigated effects of

personal PM exposures on HRV (Chan et al. 2004; Magari et al. 2001) and one on personal CO (Tarkiainen et al. 2003).

Liao et al. (1999) showed that the largest inverse associations between non-ambulatory HRV measures and $PM_{2.5}$ were for subjects with a history of cardiovascular conditions, although the number subjects (18) was small and the specific illnesses were not separated (not shown in Table 1). Another study of 56 elderly subjects showed inverse associations of non-ambulatory high and low frequency HRV with indoor and outdoor 24-hr gravimetric $PM_{2.5}$ collected in a retirement home (Creason et al. 2001, not shown in Table 1). Using hourly ambient $PM_{2.5}$ data, they briefly reported that models using prior 4-hr average $PM_{2.5}$ and time lagged 4-hr $PM_{2.5}$ were similar in magnitude to effects of the 24-hr $PM_{2.5}$ averages, suggesting a mixture of short-term and cumulative effects. Holguin et al. (2003) studied 34 elderly nursing home residents living in Mexico City and showed a strong decrease in the high frequency component of HRV with high ambient $PM_{2.5}$ exposure, and the association was stronger for indoor home $PM_{2.5}$. Those with hypertension had the largest reductions in HRV (Table 1). Pope et al (1999) also used ambulatory HR monitoring in seven elderly subjects with respiratory and cardiovascular disease before, during, and after episodes of elevated pollution. They found ambient PM_{10} was associated with decreased in the SD of normal RR intervals (SDNN), a time domain measure of overall HRV. Howver, thay also found but an increase in the square root of the mean of squared differences between adjacent NN intervals (r-MSSD) (time domain measurement that corresponds to high frequency variability and parasympathetic tone). A larger study using ambulatory ECG monitors by Pope et al. (2004b) found that ambient $PM_{2.5}$ was associated with a decrease in both SDNN and r-MSSD in 88 elderly subjects in Utah (Table 1). Magari et al. (2001) studied 40 workers occupationally exposed to welding fumes and residual oil fly ash with 24-hr monitoring using ambulatory heart rate (HR)

monitors and personal real-time $PM_{2.5}$ measurements from a TSI Inc. DustTrak (Shoreview, MN) (Table 1). They found significant decreases in standard deviation of average 5-min normal-to-normal intervals (SDANN) in relation to increases in prior 1-hr moving averages of $PM_{2.5}$. They also found increasingly greater decreases in SDNN for higher $PM_{2.5}$ across longer $PM_{2.5}$ averaging times up to 9 hours. Magari et al. (2001) suggested inhaled particles directly affects autonomic function through a sympathetic stress response, represented by their acute response finding, and/or secondarily through airway inflammation and cytokine release into the circulation, represented by their cumulative response finding. Riediker et al. 2004 placed portable air-quality monitors in patrol cars of nine healthy male North Carolina Highway Patrol troopers who wore ambulatory ECG monitors (Table 1). In-vehicle $PM_{2.5}$ was positively associated with ectopic beats, heart beat cycle length, HF HRV and SDNN.

Chan et al. (2004) conducted the only study to date to assess the relationship between HRV and particle number concentrations (dominated by UFP) for particles 0.02-1.0 μm in diameter ($NC_{0.02\text{-}1}$) (Table 1). They followed9 young healthy adults (2 females) and 10 elderly male subjects with obstructive lung function impairment. This was also the first study to examine the effects of personal exposure to UFP on HRV. Subjects were monitored over only 10 daytime hours using a P-Trak Ultrafine Particle Counter (TSI Inc., Shoreview, MN) for $NC_{0.02\text{-}1}$. Subjects also wore ambulatory ECG monitors for continuous 5-min beat-to-beat intervals to assess HRV. Using linear mixed effects models they found decreases in HRV indices (SDNN and r-MSSD) were associated with exposure to one to four-hr moving averages of $NC_{0.02\text{-}1}$ before the 5-min HRV measurements, adjusting for age, sex, body mass index, environmental tobacco smoke exposure and temperature (Table 1). Associations were stronger for the elderly panel, with the strongest effects from two-hr average $NC_{0.02\text{-}1}$. These results along with Magari et al. (2001) suggest that effect of personal PM

exposure on autonomic function is acute, although the monitoring period (10 hr) was too short in Chan et al (2004) to assess longer-term effects.

Tarkiainen et al. (2003) studied six patients with CHD for one day per week for three weeks with continuous personal CO exposure monitors, ambulatory ECG monitoring for HRV and time-activity diaries and found r-MSSD increased in relation to high CO exposures (> 2.7 ppm peaks lasting 17 min, SD 8 min) (Table 1). This result contrasted results of most studies using PM exposures except Pope et al (1999). No particle data was available, but it is again important to note that outdoor CO at sites close to dense traffic is highly correlated with UFP (Zhu et al. 2002). It is conceivable that CO and/or UFP increases vagal control and induces bradyarrhythmias.

In the one study of arrhythmias and air pollution, investigators followed 100 subjects in eastern Massachusetts with implanted defibrillators (Peters et al. 2000, Table 1). They found patients with ten or more defibrillator discharge interventions for cardiac arrhythmias experienced increased arrhythmias in association with outdoor ambient NO_2, CO, black carbon, but $PM_{2.5}$ was less strongly related. The most robust association was found for NO_2, which may have been a marker for local traffic-related pollution, whereas particle mass may have been additionally influenced by other sources. Exposure was represented by only one Boston monitoring site.

Systemic Inflammation and Thrombosis

The view that air-pollution induced airway inflammation triggers systemic hypercoagulability (Seaton et al. 1995) has been supported in recent epidemiologic studies. It is relevant in this regard that compared with unaffected people, patients with CHD (Mendall et al. 1997; Lagrand et al. 1999; Stec et al. 2000; Woods et al. 2000), or a complication of CHD, CHF (Pye et al. 1990; Torre-Amione et al. 1996) have increased levels of inflammatory cytokines such as interleukin-1β (IL-1β)

and interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). They also have increased levels of circulating acute phase proteins such as CRP and fibrinogen. In patients with CHD, CRP is also a strong independent predictor of future coronary events (Rifai et al. 2001). Cohort studies have shown that levels of acute phase proteins, cytokines and hemostatic factors indicative of a thrombophilic state or endothelial activation are elevated at baseline in subjects at risk for future coronary occlusion or cardiovascular mortality (Cushman et al. 1999; Danesh et al. 2000; Folsom et al. 2001; Harris et al. 1999; Haverkate et al. 1997; Jager et al. 1999; Kuller et al. 1996; Lind et al. 2001; Malik et al. 2001; Ridker et al. 2000, 2001; Ridker 2001; Thompson et al. 1995). Air pollutant exposures that lead to acute increases in already elevated levels of inflammatory and hemostatic factors may also precipitate adverse health outcomes. This is a strong possibility in patients with diagnosed or underlying CHD, a population most likely driving the time series associations. In addition, high air pollutant exposures that lead to chronic or repeated increases in systemic inflammation through oxidative stress responses to ROS may promote the progression of atherosclerosis in susceptible individuals.

Recent studies have shown acute associations between air pollutant exposures and systemic responses indicating inflammation and hypercoagulability. Seaton et al. (1999) studied 112 elderly individuals and used one day of personal PM_{10} data per person to predict the remaining two days using ambient (city center) PM_{10} data (Table 1). Results showed inverse associations of estimated personal PM_{10} with albumin-adjusted hemoglobin, packed cell volume, red blood cell count, platelets and factor VII levels. They found no associations between PM_{10} and IL-6 or white blood cell count. Only ambient PM_{10} was positively associated with C-reactive protein (CRP) concentrations, but it was also inversely associated with fibrinogen. The authors hypothesized that particles enter lung endothelial cells or erythrocytes and subsequently influence red cell

adhesiveness leading to peripheral sequestration of red cells. Contrasting results were found by Schwartz (2001) who used health data from the Third National Health and Nutrition Examination Survey (NHANES III) in the United States (Table 1). Results showed that outdoor PM_{10} levels on the day of subject visits or previous day was positively associated with fibrinogen levels, and counts of platelets and white blood cells. Fibrinogen increased by 13 μg/dL (95% CI: 4.6-22.1) for an interquartile range change in PM_{10} of 26 $\mu g/m^3$. PM effects were independent of gaseous pollutants. Schwartz (2001) argued that the NHANES III results were consistent with data in controlled human exposure (Ghio et al. 2000) and animal studies (Gardner et al. 2000) that showed increased plasma fibrinogen following particle exposures. Pekkanen et al. 2000 found no association between PM_{10} and fibrinogen using cross-sectional data from another cohort study 7205 subjects in London. However, they did find associations between fibrinogen and two pollutant gases, NO_2 and CO, but not SO_2 or O_3. An epidemiologic studies in Augsburg, Germany has also shown positive associations of ambient air pollution with plasma viscosity (Peters et al, 1997a) and with C-reactive protein (CRP) concentrations (Peters et al, 2001b, Table 1). Another study of people exposed to forest fire smoke showed increased circulating levels of IL-1β and IL-6 (Van Eeden et al. 2001, not shown). A panel study by Pope et al. (2004b, Table 1) with 88 elderly subjects in Utah showed a 0.81 mg/dL CRP increase in association with a 100 $\mu g/m^3$ increase in ambient $PM_{2.5}$. There was no association with white or red blood cell counts, platelets, or whole-blood viscosity. Riediker et al, 2004 (discussed above) assessed the relationship between in-vehicle PM exposure and markers of inflammation in nine healthy male state troopers. An in-vehicle 10 $\mu g/m^3$ $PM_{2.5}$ increase was associated with decreased lymphocytes (-11%), increased red blood cell indices (1%), neutrophils (6%), C-reactive protein (32%), and von Willebrand factor (12%).

Summary and Biological Plausibility

In summary, only three studies to date have directly evaluated impacts on cardiovascular health by UFP or particle number concentration (Chan et al. 2004; Ibald-Mulli et al. 2004; Pekkanen et al. 2002). Results of Pekkanen et al. (2002) showing ST segment depression in relation to UFP is the most compelling finding. Associations of ambient $NC_{0.01\text{-}0.1}$ with ST segment depression were independent of ambient $PM_{2.5}$, but it is unclear whether the ambient exposure data represented personal UFP exposures of subjects. Other indirect evidence that components of fossil fuel combustion are important come from studies using surrogate measures of particle composition such as black smoke, proximity of homes to traffic, or source apportionment data. Epidemiologic associations for pollutant gases also appear to add to the notion that cardiovascular effects may be linked to primary products of combustion emissions that include UFP.

Because hypertension, ST segment depression and cardiac arrhythmias are well-known risk factors for cardiac morbidity and mortality, the above findings of acute associations with PM from individual-level studies are relevant to the reported findings of time series and cohort investigations of mortality and hospital morbidity. However, mixed findings for BP have not provided a coherent view of particle effects. Findings for HRV are largely consistent in finding a decrease in HRV except for the increase in r-MSSD with ambient PM among elderly subjects found by Pope et al (1999) and increased HF HRV for in-vehicle PM among healthy men found by Riediker et al. (2004). The clinical importance of HRV to cardiovascular disease is unclear though (Task Force 1996), and many technical issues regarding the influence of respiratory patterns (respiratory sinus arrhythmia) and psychosocial stress (both unmeasured in the reviewed studies) remain unresolved (Sloan et al. 1994).

The reviewed epidemiological studies on circulating biomarkers of effect show inconsistent relationships between air pollution and blood markers of inflammation and hypercoagulability, possibly because all but two studies used ambient exposure to PM. Seaton et al. (1999) and Riediker et al. (2004) are currently the only studies that used any personal PM exposure measurements, but results are not consistent. In addition, the reviewed studies of circulating biomarkers did not target people with cardiovascular diseases, who are expected to be among the most susceptible population as indicated in the time series investigations.

The main limitation of most epidemiologic studies is exposure misclassification from dependence on central site rather than personal or microenvironmental exposure data. However, studies reported above that do have personal exposure data also have limited numbers of subjects or days monitored. In general, some major methodological issues that remain involve choice of susceptible populations, personal exposure assessment, and timing of measurements to assess the temporality of exposure-dose-response relationships.

Despite the inconsistencies in epidemiologic data, there are sound postulated mechanisms that support the biological plausibility of many of the findings. Airway inflammation from PM likely involves inhalation of agents leading to the deposition or production in lung tissue of ROS. The ROS then induce subsequent oxidant injury and inflammatory responses (Pritchard et al. 1996; Schreck et al. 1991) both in the lungs and systemically. Inhalation of particle-bound airborne transition metals (copper, iron, nickel and vanadium) can lead to the production of ROS in lung tissue. Residual oil fly ash containing high concentrations of transition metals but low in organic compounds have been shown to induce in vitro increases in IL-6 mRNA in human epithelial cells (Quay et al. 1998). Dogs exposed to concentrated ambient particles from Boston air showed increased BAL macrophages and increased circulating neutrophils in relation to a vanadium/nickel

factor, but no associations were shown with total mass (Clarke et al. 2000). This suggests pollutant composition was important.

Organic constituents of PM are also capable of generating ROS. Nel et al. (2001) have presented evidence that polycyclic aromatic hydrocarbons (PAH) from diesel exhaust particles (DEP) and oxidized derivatives of PAHs, such as quinones, lead to the generation of ROS and subsequent oxidant injury and inflammatory responses, including the production of nuclear transcription factor-κB (NFκB). NFκB increases the transcription of cytokines and acute phase proteins (Schreck et al. 1991). Evidence has been presented that DEP induces a broad polyclonal activation of cytokines from an adjuvant-like activity of DEP PAH (Diaz-Sanchez 1996; 1997; Fujieda 1998; Nel et al. 1998; 2001). Human pulmonary responses to DEP include increased neutrophils and B-lymphocytes in lavage fluids, increased expression of endothelial adhesion molecules ICAM-1 and VCAM-1 in bronchial biopsies, and increased neutrophils and platelets in peripheral blood (Salvi et al. 1999). Such DEP-induced effects from oxidative stress mechanisms would be expected to lead to increased systemic hypercoagulability, but to date supporting data in humans is limited.

Epidemiologic evidence in humans that PM exposure increases biomarkers of oxidative stress in blood is limited to one study of 50 healthy young adults in Copenhagen using air samplers carried by subjects (Sorensen et al, 2003). They found a positive association between personal black carbon exposure and 2-aminoadipic semialdehyde in plasma proteins (PLAAS, a protein oxidation product). However, no association with personal $PM_{2.5}$ mass was found, suggesting that traffic-related causal components may have been better represented by black carbon than by particle mass. A lipid peroxidation product (malondialdehyde), as well as RBC and hemoglobin concentrations, were positively associated with $PM_{2.5}$ exposure in women only.

There are also plausible linkages between pulmonary and cardiovascular responses to PM. Airway inflammatory responses have been demonstrated in animals exposed to particulate air pollutants (EPA, 2003). As discussed above, there is growing evidence that airway responses may trigger systemic inflammation and hypercoagulability. In addition, PM can induce neurogenic inflammation in the lungs from activation of capsaicin-sensitive irritant receptors leading to the release of tachykinins from sensory terminals and then airway inflammation and bronchoconstriction (Veronesi and Oortgiesen, 2001). This response could then affect cardiovascular autonomic function (Carr and Undem, 2001; Yeates, 2000) but it is not yet clear to what extent these mechanisms explain epidemiologic findings of air pollutant associations with cardiac rhythm and BP. There is limited evidence for an effect of tachykinins on cardiac function (Maggi 1996). In addition, the linkage between airway inflammation, cytokine/chemokine release and autonomic stress response has not been directly demonstrated in humans. There are some *in vitro* data linking actions of proinflammatory cytokines IL-1β and TNF-α to myocardial cell changes in contractility and action potentials (DeMeules et al. 1992; Finkel et al. 1992; Li and Rozanski, 1993; Yokoyama et al. 1993) and to induction of arrhythmias (Weisensee et al. 1993).

There is experimental data indirectly supporting a linkage between cellular inflammation in the lungs and cardiovascular responses to air pollutants. An experiment in hyperlipidemic rabbits showed that intrapharyngeal installation of ambient urban PM_{10} led an increase in circulating PMNs and caused an increase in the volume fraction of atherosclerotic lesions, which correlated with the number of alveolar macrophages that phagocytosed PM_{10} in the lung ($r = 0.5$) (Suwa et al. 2002). Particle-induced airway inflammation and translocation of ultrafine particles and other pollutants into the circulation could lead to an increase in thrombogenic and inflammatory activity in the

blood, and to a disturbance in cardiovascular function. These extra-pulmonary effects are expected to increase the risk of adverse cardiovascular outcomes such as hospitalization.

Other evidence links airway inflammation with cardiovascular effects. Cohort data has shown links of COPD with CHD risk independent of other risk factors (Jousilahti et al. 1999; Wedzicha et al. 2000), suggesting that pulmonary inflammatory processes may have pro-inflammatory effects on the vascular endothelium. This could occur in individuals with asthma or COPD who have depleted antioxidant defenses from oxidative stress as compared with normal subjects, and their defenses are further lowered during disease exacerbations (Rahman et al. 1996). Zanobetti & Schwartz (2000a) have shown that a positive association between hospital admissions for cardiovascular diseases and ambient air pollution was nearly doubled in elderly patients admitted with concurrent respiratory infections. Diabetics appear to be another susceptible group, with stronger associations between cardiovascular hospital admissions and ambient air pollution (Zanobetti & Schwartz, 2001).

Several excellent reviews of experimental data examining acute pulmonary and cardiovascular responses to inhaled ultrafine and fine particles have proposed pathophysiological mechanisms (ATS, 1999; Dhalla et al. 2000; Donaldson et al. 2001; Godleski et al. 2000; MacNee & Donaldson, 2000; Nel et al. 2001; Utell & Frampton, 2000; van Eeden and Hogg, 2002; Utell et al 2002). We have synthesized this and other data into the following proposed sequence of events for UFP that link pulmonary and cardiovascular endpoints as follows (Figure 1). Most of these mechanisms likely also apply to larger PM size fractions, particularly soluble components of $PM_{2.5}$, and retained non-soluble particles in the lung that may stimulate the bone marrow to induce similar systemic responses (van Eeden and Hogg, 2002).

1) UFP exposure is followed by high pulmonary deposition (ICRP, 1994; Daigle et al. 2003; Chalupa et al. 2004). Ultrafine particles and associated air toxics translocate to the interstitium and gain entry into the circulation (Nemmar et al. 2002, 2004; Oberdörster et al. 2002).

2) Redox active components of PM lead to the production of ROS in various cells in the lungs, blood and vascular tissues.

3) This is followed by oxidative stress responses in pulmonary epithelium and pulmonary vascular endothelium and in extrapulmonary vascular endothelium, leading to the production of oxidized phospholipids (especially LDL), lipid peroxidation (e.g., 8-iso-PGF2α), reduced antioxidant capacity (e.g., increase in the ratio of oxidized to reduced glutathione), and the production of superoxide anions by endothelial NADPH oxidase, all of which likely contributes to atherogenesis. Genetic polymorphisms in key metabolic enzymes likely play a role in susceptibility.

4) Pulmonary and extrapulmonary peripheral vascular oxidative stress result in the activation and mobilization of mononuclear leukocytes and the expression of NFκB, followed by increases in pro-inflammatory cytokines (e.g., IL-1β, IL-6 and TNF-α) and endothelial cell activation.

5) Emigration of inflammatory cells from blood to tissue sites involves upregulation of adhesion molecules (VCAM-1, ICAM-1) on vascular endothelium and circulating leukocytes.

6) Increased release of cytokines by activated mononuclear cells in the lungs and in the blood leads to initiation of hepatic synthesis of acute phase proteins (e.g., CRP and fibrinogen).

7) A hypercoagulable state then occurs with platelet activation, hemostasis and blood clot formation followed by fibrinolytic activity; this increases the risk of a coronary event. Cytokines may also have direct effects on cardiac function.

8) Endothelial cell activation also leads the expression of endothelin-1, which induces vasoconstriction, and increased systolic and diastolic BP, and the expression of extracellular superoxide dismutase (SOD). SOD catalyzes superoxide ($O_2^{\cdot -}$) to H_2O_2, which lowers endothelial NO-induced vasodilation. Neuroinflammatory responses involving tachykinins and catecholamines may also affect cardiovascular autonomic tone.

9) The systemic inflammatory response also stimulates the bone marrow to release leukocytes and platelets, and polymorphonuclear leukocytes increasingly sequester in pulmonary capillaries to induce more inflammation.

Conclusion

As presented in this article, numerous studies have implicated particulate air pollution as an important contributor to morbidity and mortality from cardiovascular causes. Most of this data have been epidemiological and have utilized available air pollution data from governmental monitoring stations. Because such data are collected to meet regulatory standards, they may not meet the needs of researchers trying to understand the causal pollutant components that lead to specific adverse health effects. UFP and related toxic constituents and precursors are examples of air pollutants that have not been fully investigated, in part due to lack of available data. To date, data from epidemiologic studies indirectly implicate traffic- and other combustion-related pollutants, which include UFP. Exposure assessment issues for UFP are complex and need to be considered before undertaking epidemiologic investigations of UFP health effects (Sioutas et al. in press).

A large body of evidence shows that inflammation and oxidative stress are related to both acute changes in cardiovascular health and chronic processes including atherosclerosis. It is likely that redox active components in UFP from fossil fuel combustion reach target sites in the lungs,

vasculature, and heart to induce inflammation and oxidative stress, adding to the burden of other known lifestyle risk factors for cardiovascular disease such as diet, tobacco smoke and stress.

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Table 1: Cardiovascular effects[a] associated with personal and ambient air pollution exposure: Selected studies

Studies	Design and Population	Outcomes	Findings for PM Mass and Components	Findings for Gases
Cohort and Cross-sectional Studies				
Dockery et al. 1993	Cohort study examining ambient air pollution exposure and mortality in 8111 adults in six US cities with 14 to 16 years of follow-up.	Cardiopulmonary mortality	Compared to the least polluted city, the most polluted city had an adjusted RR for cardiopulmonary mortality of 1.37 (95% CI: 1.11, 1.68).	No association with O_3, but SO_2 and NO_2 tracked between-city trends in PM concentrations.
Pope et al. 2004a	Cohort study examining ambient PM exposure and cardiovascular mortality in 319,000-500,000 persons in the American Cancer Society study, with 16 years follow-up across U.S. urban areas.	Cardiovascular mortality: ischemic heart disease, dysrhythmias, heart failure, and cardiac arrest.	A 10 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with 8-18% increases in mortality due to ischemic heart disease, dysrhythmias, heart failure, and cardiac arrest.	Not assessed
Abbey et al. 1999	Cohort study examining ambient PM_{10} exposure, total suspended sulfates, SO_2, O_3, and NO_2 to mortality in 6,338 nonsmoking California Seventh Day Adventists with 19 yr follow-up.	Cardiopulmonary mortality	No associations.	No associations.
Hoek et al. 2002	Cohort study examining ambient traffic related air pollutant exposure (black smoke and NO_2) and cause specific mortality in 5000	Cardiopulmonary mortality	Cardiopulmonary mortality was associated with living near high traffic density (100 m to freeway or 50 m to major urban road) adjusted RR= 1.95 (95% CI: 1.09, 3.52), and was	Cardiopulmonary mortality was similarly associated with an increase of 30 $\mu g/m^3$ background plus

Studies	Design and Population	Outcomes	Findings for PM Mass and Components	Findings for Gases
	persons with 8 years follow-up in the Netherlands Cohort Study on Diet and Cancer.		associated with an increase of 10 $\mu g/m^3$ black smoke from background (central sites) + local sources (street proximity), RR 1.71 (95% CI: 1.10, 2.67).	local NO_2, RR 1.81 (95% CI: 0.98, 3.34)
Kunzli et al. 2004	Cross-sectional study on the relationship between ambient $PM_{2.5}$ and carotid artery intima-media thickness (CIMT) using baseline data from two clinical trials in Los Angeles. Annual mean $PM_{2.5}$ exposure was estimated using data from 23 monitoring stations linked to home addresses with geostatistical models.	Carotid artery intima-media thickness	For each increase of annual mean 10 $\mu g/m^3$ $PM_{2.5}$, CIMT increased by 5.9% (95% CI: 1, 11%). Adjustment for age reduced the coefficients, but further adjustment for covariates indicated robust estimates in the range of 3.9 to 4.3%.	Estimates for O_3 linked to zip code centroids were positive in relation to CIMT but not significant and smaller than $PM_{2.5}$.
Cardiac Ischemia and Related Outcomes				
Pekkanen et al. 2002	Panel study examining ambient PM, NO_2, CO exposure and ischemia during 342 submaximal exercise tests in 45 subjects with CHD in Helsinki, Finland.	Electrocardio-graphic ST segment depression over 0.1 mV	Increased risk for ST depression (72 events) was associated with a change of lag 2 1000 particles/cm^3 of accumulation mode PM ($NC_{0.1-1}$) OR=3.29 (95% CI: 1.57, 6.92), and 10,000 particles/cm^3 of UFP ($NC_{0.01-0.1}$) OR=3.14 (95% CI: 1.56, 6.32). UFP was independent of associations with a 10 $\mu g/m^3$ increase in lag 2 $PM_{2.5}$ [OR=2.84, 95% CI: 1.42, 5.66).]	NO_2 and CO were also associated with an increased risk for ST depression.

Studies	Design and Population	Outcomes	Findings for PM Mass and Components	Findings for Gases
de Hartog et al, 2003	Panel study examining ambient exposure to PM and NO_2, SO_2 and CO on HRV and BP in 131 subjects with CHD in Helsinki, Finland, Amsterdam, the Netherlands, Erfurt, Germany.	Cardiorespiratory symptoms: chest pain, shortness of breath, avoidance of activities	A 10 μg/m^3 increase in $PM_{2.5}$ associated with shortness of breath and avoidance of activities.	Not assessed
Peters et al. 2004	Case-crossover study examining ambient traffic related air pollution exposure and myocardial infarction in 691 subjects from the Augsburg Myocardial Infarction Registry who had survived 24 h post infarct. Time-activity diary data on activities during the four days before symptom onset was used to assess traffic exposures.	Myocardial Infarction	Exposure to traffic was associated with onset of myocardial infarction one hour afterward, OR =2.92 (95% CI: 2.22, 3.83). A significant association was also seen for exposure to traffic two hours before onset, and there was evidence for effects up to six hours. Key exposures influencing overall associations with traffic included times spent in cars and in public transportation. Associations changed minimally adjusting for exercise, and there was no confounding by reports of extreme anger or joy.	As with PM, gases were not directly assessed, but traffic exposures involve pollutant gases as well as particles.
Blood Pressure (BP)				
Linn et al. 1999	Panel study in Los Angeles, California examining BP and lung function in 30	BP	Systolic BP increased 0.172 mm Hg for every 1 μg/m^3 increase in ambient lag 1 PM_{10} (p = 0.006). Diastolic BP	No association of BP with exposure to central site O_3, NO_2, or CO.

Studies	Design and Population	Outcomes	Findings for PM Mass and Components	Findings for Gases
	subjects with COPD, with only four consecutive days of air sampling: personal exposure to $PM_{2.5}$, indoor and outdoor home $PM_{2.5}$ and PM_{10}, and ambient PM_{10}, O_3, NO_2, and CO.		increased 0.095 mm Hg for every 1 $\mu g/m^3$ increase in PM_{10} ($P = 0.03$). Outdoor home PM_{10} was similarly associated with BP, but no significant associations were reported for $PM_{2.5}$ or any indoor or personal PM measurement.	
Brauer et al. 2001	Panel study examining personal exposure over seven nonconsecutive days to $PM_{2.5}$ and sulfate, and ambient exposure to ambient $PM_{2.5}$, PM_{10}, sulfate, and gaseous pollutants, in relation to BP, HRV, and lung function in 16 COPD patients in Vancouver, Canada.	BP, HRV, supraventricular ectopic heartbeats (SVE)	Weak associations were observed between particle concentrations and increased SVE and with decreased systolic BP. Ambient PM_{10} had the largest effect on cardiovascular endpoints and the only statistically significant association (SVE). Use of personal exposure measurements did not show a larger or more consistent effect.	CO was inversely associated with systolic BP and reduced estimates for ambient PM.
Ibald-Mulli et al. 2001	Retrospective analysis examining the relationship between ambient air pollution exposure (TSP, SO_2 and CO) and blood pressure in 2607 men and women ages 25-64 y from a general population survey in Augsburg, Germany.	Systolic BP	A 90 $\mu g/m^3$ increase in TSP was associated with an increase in systolic BP of 1.79 mm Hg (95% CI: 0.63, 2.95). In subgroups with high plasma viscosity levels or increased heart rates, systolic BP increased by 6.93 mm Hg (95% CI: 4.31, 9.75) and 7.76 mm Hg (95% CI: 5.70, 9.82) in association with TSP, respectively	An 80 $\mu g/m^3$ increase in SO_2 was associated with an increase in systolic BP of 0.74 mm Hg (95% CI: 0.08, 1.40).
Ibald-Mulli et al. 2004	Panel study examining ambient exposure to PM and NO_2, SO_2 and CO on HRV	BP and HR (Ibald-Mulli et al. 2004);	A small decrease in systolic BP (–0.72 mm Hg, 95% CI: –1.92, 0.49) and diastolic BP (–0.70 mm Hg, 95% CI:	The magnitude and significance of inverse BP associations with CO were

Studies	Design and Population	Outcomes	Findings for PM Mass and Components	Findings for Gases
	and BP in 131 subjects with CHD in Helsinki, Finland, Amsterdam, the Netherlands, Erfurt, Germany.		–0.02, –1.38) was found to be associated with a 5-day average increase of 10,000 ultrafine particles/cm^3 ($PM_{0.01-0.1}$). Slightly stronger and more significant associations were found for accumulation mode particle number concentration ($PM_{0.1-1.0}$), but smaller associations were found for a 10 $\mu g/m^3$ increase in $PM_{2.5}$ mass. Small decreases in HR were also found for PM exposures.	similar to $PM_{0.1-1.0}$. A small decrease in HR (–0.40 beats/min, 95% CI: –0.82, 0.01) was found for an increase of lag 1 5 $\mu g/m^3$ SO_2.
Zanobetti et al. 2004	Panel study examining the association between ambient $PM_{2.5}$ and blood pressure among 62 patients with pre-existing heart disease using data from 631 repeated visits for cardiac rehabilitation in Boston.	BP	Increasing from the 10^{th} to the 90^{th} percentile in 5-day mean $PM_{2.5}$ resulted in a 2.8 mm Hg (95% CI: 0.1, 5.5) increase in systolic, a 2.7 mm Hg (95% CI, 1.2 to 4.3) increase in diastolic, and a 2.7-mm Hg (95% CI: 1.0, 4.5) increase in mean arterial blood pressure.	Not assessed.
Autonomic Control of Cardiac Rhythm				
Holguin et al. 2003	Panel study in Mexico City examining indoor and outdoor nursing home measurements of $PM_{2.5}$, and ambient exposure to O_3, NO_2, CO, SO_2 in relation to HRV in 34 elderly residents followed	HRV, frequency domain	A 10 $\mu g/m^3$ increase in predicted personal $PM_{2.5}$ was associated with a 5.0% decrease in high frequency HRV (β = –0.049, 95% CI: –0.090, –0.007). Associations with indoor $PM_{2.5}$ were stronger than outdoor home $PM_{2.5}$. Among 13 subjects with hypertension, the association with predicted personal	O_3 was inversely associated with high and low frequency HRV among 13 subjects with hypertension (2% decrease per 10 ppb O_3), but this association was confounded by $PM_{2.5}$.

Studies	Design and Population	Outcomes	Findings for PM Mass and Components	Findings for Gases
	every other day for 3 months. Personal $PM_{2.5}$ was predicted using indoor and outdoor home $PM_{2.5}$ plus time-activity data		$PM_{2.5}$ was stronger (–7.1%).	
Pope et al. 2004b	Panel study of ambient exposure to PM and HRV and blood markers in 88 elderly subjects living in Salt Lake, and Provo/Orem Utah	HRV and blood markers of inflammation (see below)	A 100 μg/m^3 increase in $PM_{2.5}$ was associated with a 35 (SE = 8) msec decrease in SDNN, and a 42 (SE = 11) msec decrease in r-MSSD	Not assessed
Magari et al. 2001; 2002a; 2002b	Panel study examining personal exposure to PM in relation to HRV in 20 (Magari et al. 2002a) 40 (Magari et al. 2001) and 39 (Magari et al. 2002b) healthy boilermakers exposed to welding fumes and residual oil fly ash.	HRV	Each 100 μg/m^3 increase in 3-hr average $PM_{2.5}$ (laser photometer light scatter) was associated with a 1.4% (95% CI: –2.1, –0.6%) decrease in 5-min SDNN in the 20 subjects (Magari et al. 2002a). In the 40 subjects, each 1 mg/m^3 increase in 4-hr average $PM_{2.5}$ was associated with a 2.66% (95% CI: –3.75, –1.58%) decrease in 5-min SDNN (Magari et al. 2001). However, in 39 of the same subjects, $PM_{2.5}$ metals on filters, lead and vanadium, were associated with an increase in workday average of the 5-min SDNN (Magari et al. 2002b).	Not assessed
Riediker et al. 2004	Panel study of in-vehicle exposure to PM and HRV and blood markers of inflammation in 9 healthy	HRV and blood markers of inflammation (see below)	In-vehicle 10 μg/m^3 $PM_{2.5}$ increase was associated with increased ectopic beats throughout exposure (20%, $p = 0.005$). $PM_{2.5}$ was positively associated with	NO_2 and CO were not significant

Studies	Design and Population	Outcomes	Findings for PM Mass and Components	Findings for Gases
	male North Carolina Highway Patrol troopers.		heart beat cycle length (6%, $p = 0.01$) as well as HF HRV and SDNN the next morning following exposure.	
Chan et al. 2004	Panel study in Taipei, Taiwan examining personal exposure to submicrometer particles and HRV over one 16-hr daytime period in 9 young healthy adults ages 19-29 y (2 females) and 10 older male subjects ages 42-97 y with lung function impairments ($FEV_1/FVC < 85\%$).	HRV	Personal exposure to $NC_{0.02-1}$ was associated with decreased in both time-domain and frequency-domain HRV indices. In young subjects, a 10,000 particles/cm^3 increase in the last 1-4 hr average $NC_{0.02-1}$ was associated with 0.68-1.35% decrease in SDNN, 1.85-2.58% decrease in r-MSSD. In the older panel they found 10,000 particles/cm^3 increase in the last 1-3 hr average $NC_{0.02-1}$ was associated 1.72-3.00% decreases in SDNN, and 2.72-4.65% decreases in r-MSSD. There were similar associations for high and low frequency-domain indices.	Not assessed
Tarkiainen et al. 2003	Panel study in Kuopio, Finland, examining personal exposure to carbon monoxide and HRV in 6 subjects with CHD followed for three separate 24-hr ambulatory monitoring periods.	HRV	Not assessed	r-MSSD increased by 2.4 ms ($p = 0.03$) with exposure to CO (> 2.7 ppm).
Peters et al. 2000	Panel study of arrhythmias in 100 subjects in eastern Massachusetts with implanted defibrillators	Defibrillator discharge interventions for ventricular	Only 6 subjects with ≥10 defibrillator discharges had increased arrhythmias associated black carbon and $PM_{2.5}$, which showed a weaker association.	26-ppb increase in NO_2 lagged 1 d was associated with increased defibrillator interventions in the full

Studies	Design and Population	Outcomes	Findings for PM Mass and Components	Findings for Gases
	(63,628 person-days of follow-up) with ambient measurements of PM mass, black carbon, NO_2, CO, O_3 and SO_2	tachycardias or fibrillation (33 subjects with at least one).	Both PM metrics were confounded by NO_2, but the effect estimate of NO_2 was unchanged.	panel (OR 1.8; 95% CI: 1.1, 2.9). Subjects with ≥10 defibrillator discharges had increased arrhythmias associated with CO and NO_2. across several lags
Systemic Inflammation and Thrombosis				
Seaton et al. 1999	Panel study examining 3 day* personal exposure and city center ambient exposure to PM_{10} on hematological factors in 112 elderly subjects in Belfast and Edinburgh, UK. *(personal exposure estimated from a one 24 hour personal exposure measurement)	Hematological factors: hemoglobin, packed red cells, red blood cell count, platelets, white blood cell count, CRP, fibrinogen, factor VII, interleukin-6	An increase of 100 μ/m^3 in personal PM_{10} and ambient PM_{10} exposure resulted in significant decreased mean percentage changes of ≤ 1% in hemoglobin concentration, packed cell volume, and red blood cell count. Only personal PM_{10} was associated with an 11% decrease in platelets and a 7% decrease in Factor VII. CRP increased with ambient PM_{10} (+147%, 95% CI: 20, 477), but not with personal PM (p = 0.73). Fibrinogen decreased with ambient PM_{10} (-9%, 95% CI: -19, 0).	Not assessed
Schwartz et al. 2001	Cross-sectional study examining the relationship between ambient PM_{10}, NO_2, SO_2, and blood biomarkers using data from a cohort study (NHANES III).	Fibrinogen, and platelet and white blood cell counts	For an interquartile range change in PM_{10} (26 $\mu g/m^3$) the relative odds for being above the 90th percentile of fibrinogen was 1.77 (95% CI: 1.26, 2.49), platelets, 1.27 (95% CI: 0.97, 1.67) and white blood cells, 1.64 (95% CI: 1.17, 2.30).	SO2 was significantly associated with white cell counts, NO2 with platelet counts and fibrinogen, but both gases were confounded by PM_{10}.
Pekkanen et al.	Cross-sectional study examining the association between ambient PM_{10},	Fibrinogen	No association between PM_{10} and fibrinogen was seen after adjustment for confounders.	NO_2 increase from the 10^{th} to the 90^{th} percentile was associated with a 1.5%

Studies	Design and Population	Outcomes	Findings for PM Mass and Components	Findings for Gases
2000	NO_2, CO, SO_2, O_3 and fibrinogen among 7205 subjects in London at baseline enrollment in a cohort study.			higher fibrinogen concentration (95% CI: 0.4% to 2.5%). Similar increase for CO resulted in 1.5% higher fibrinogen concentration (95% CI: 0.5%, 2.5%). No association with SO_2 or O_3.
Peters et al. 2001b Peters et al. 1997a	Cohort study in Augsburg, Germany, examining relationships of ambient TSP, SO_2, and CO exposure to CRP in 631 men age 45-64 with no history of MI at their baseline assessment. There were two CRP measurements three years apart.	CRP	An increase of 26 $\mu g/m^3$ (5-day mean) in TSP increased the odds of observing a CRP level above the 80^{th} percentile, OR = 1.31 (95% CI: 1.09, 1.56). CRP and plasma viscosity (Peters et al. 1997a) were increased during an air pollution episode in 1985.	An increase of 30 $\mu g/m^3$ (5 day mean) in SO_2 increased the odds of observing a CRP level above the 90^{th} percentile, OR = 1.24 (95% CI: 1.03, 1.49).
Pope et al. 2004b	Panel study of ambient exposure to PM and HRV and blood markers in 88 elderly subjects living in Salt Lake, and Provo/Orem Utah.	HRV (see above) and CRP, white blood cell count, whole blood viscosity, granulocytes, lymphocytes, monocytes, basophils, eosinophils, red blood cells, platelets	A 100 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with a 0.81 (SE = 0.17) mg/dl increase in CRP. One subject's data had a strong influence on estimates. There was no association with other outcomes.	Not assessed

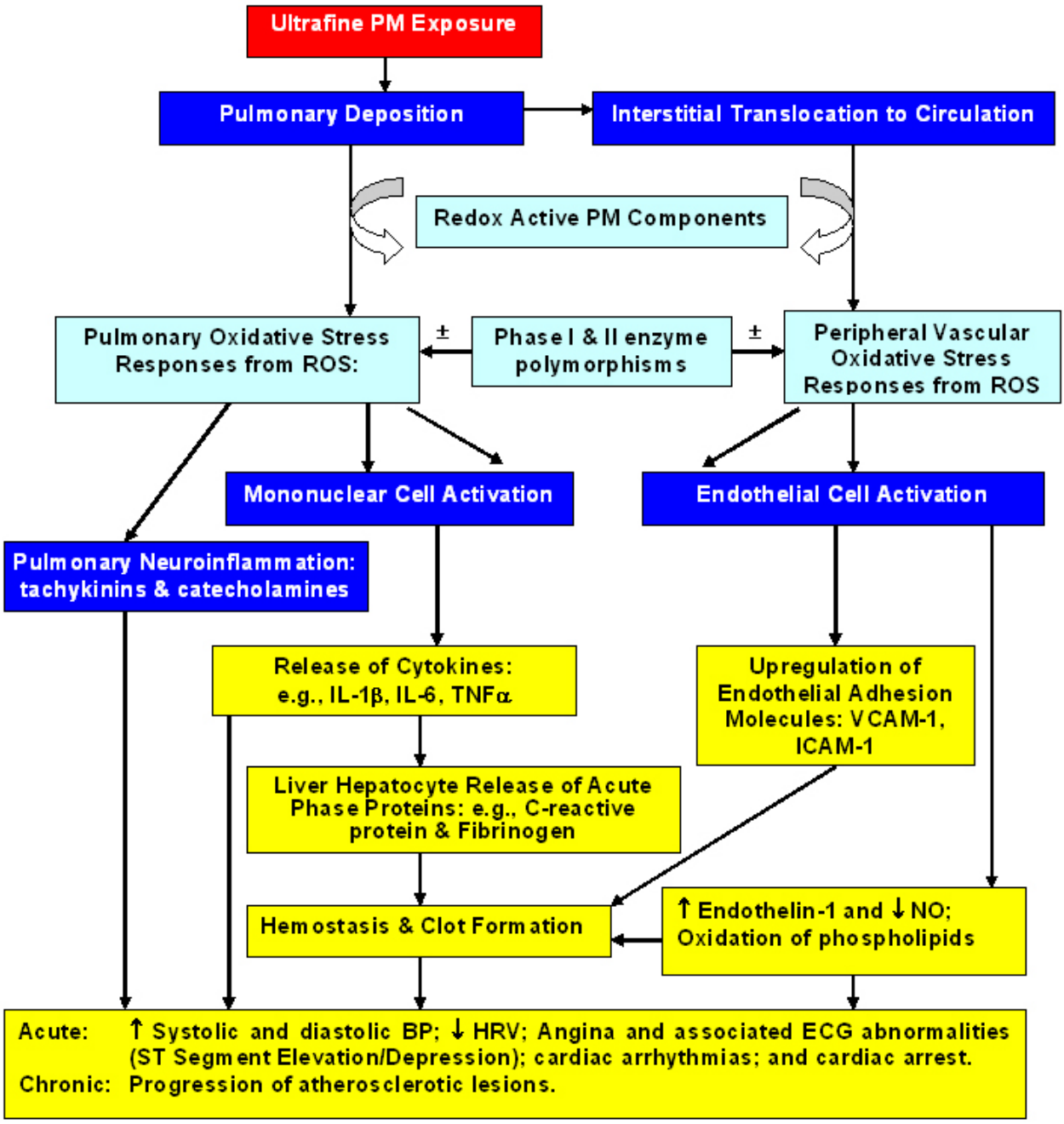
Studies	Design and Population	Outcomes	Findings for PM Mass and Components	Findings for Gases
Riediker M et al. 2004	Panel study of in vehicle exposure to PM and HRV and blood markers of inflammation in 9 healthy male North Carolina Highway Patrol troopers.	HRV (see above) and CRP, plasminogen, von Willebrand factor, Lymphocyte count, lymphocytes, neutrophils, hematocrit, red blood cell indices, uric acid	In-vehicle 10 μg/m^3 $PM_{2.5}$ increase was associated with decreased lymphocytes (−11%, $p = 0.03$), increased red blood cell indices (1%, $p = 0.03$), neutrophils (6%, $p = 0.04$), CRP (32%, $p = 0.02$), and von Willebrand factor (12%, $p = 0.02$).	NO_2 and CO were not significant

[a] The focus is on cardiovascular outcomes. Although some studies may have examined other outcomes, thay are not reported.

FIGURE LEGENDS

Figure 1. Hypothesized pathways leading to adverse cardiovascular health effects from exposure to ultrafine particles

Figure 1.


Ultrafine PM Exposure
Pulmonary Deposition
Interstitial Translocation to Circulation
Redox Active PM Components
Pulmonary Oxidative Stress Responses from ROS:
±
Phase I & II enzyme polymorphisms
±
Peripheral Vascular Oxidative Stress Responses from ROS
Mononuclear Cell Activation
Endothelial Cell Activation
Pulmonary Neuroinflammation: tachykinins & catecholamines
Release of Cytokines: e.g., IL-1β, IL-6, TNFα
Upregulation of Endothelial Adhesion Molecules: VCAM-1, ICAM-1
Liver Hepatocyte Release of Acute Phase Proteins: e.g., C-reactive protein & Fibrinogen
Hemostasis & Clot Formation
↑ Endothelin-1 and ↓ NO; Oxidation of phospholipids
Acute: ↑ Systolic and diastolic BP; ↓ HRV; Angina and associated ECG abnormalities (ST Segment Elevation/Depression); cardiac arrhythmias; and cardiac arrest.
Chronic: Progression of atherosclerotic lesions.